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Implementing a Scalable Risk-Based Monitoring Strategy

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ABSTRACT

Every organization faces unique challenges when it comes to implementing Risk-Based Monitoring (RBM). There is no 'one-size-fits-all' approach that will ensure success, as each organization has specific influencing factors such as therapeutic areas, existing processes, and technologies. This article reviews considerations to ensure not only a successful roll-out RBM but its ultimate scalability across the enterprise as well. The aim is to share best practices based on lessons learned from actual RBM initiatives. We take a look at the people, the technology, and the processes to present a clear view of what can be expected as part of the implementation process.

UNDERSTANDING THE IMPORTANCE OF RBM/RBQM

Risk-based monitoring – more aptly referred to as Risk-Based Quality Management (RBQM) – is now incorporated as a GCP expectation in the most recent ICH E6 (R2) update. The motivation for this significant paradigm shift in quality management is explained directly in the introduction section of the ICH E6 guideline. They point to a couple of key factors that have emerged over the past 15 to 20 years. First is the rapidly increasing complexity and cost of clinical research. The 2nd is the transition we've made away from largely paper-based research to the modern approach of mostly electronic/digital technologies such as EDC, ePRO, IRT and others. This move away from paper has opened up a tremendous opportunity to plan and manage clinical research more effectively and efficiently, a very timely development to address the growing crisis in research complexity and cost.

The increasing complexity and cost of research is clearly evidenced in research published by Tufts University, showing a rather dramatic increase in the size and complexity of studies from 2005 to 2015. This includes a 68% increase in the median number of procedures prescribed per patient, an 88% increase in the overall volume of patient data collected, and an actual doubling in the number of countries participating in each study¹. It is inevitable that the volume of data collected will only continue to increase – and perhaps exponentially – in the coming years with the emergence of wearable technologies for continuous patient monitoring.

This increase in complexity poses ever-greater challenges to achieving quality outcomes, as both patients and sites are burdened with managing through a myriad of requirements placed in front of them. An article published in JAMA several years ago presented an analysis of NME submissions to the FDA over a similar time period (2000 to 2012), which found that 50% of those submissions failed first cycle review². While slightly less than half of the failures were eventually approved for marketing, the average delay incurred was 14 months! And most distressing of all is possibility that up to 32% of all first-cycle failures – or up to 16% of all submissions – were failed due to issues with data quality. This is a somewhat startling finding, and one that we should find unacceptable as an industry.

An article sponsored by TransCelerate and published in the DIA Journal in 2014, presented a rigorous analysis of the impact that 100% source data verification (SDV) has on overall data quality³. And what they found was that SDV impacts only 1% of the eCRF data on average, while 15% of the total cost of clinical research is driven by SDV! It is clear then that change is needed in the way we plan and manage our clinical trials and ensure quality outcomes.

We should note that prior to the ICH E6 update, both the FDA and EMA had already provided strong endorsements to move towards RBM and RBQM – in the form of guidance documents that were finalized in 2012.

It is important to understand that Quality by Design (QBD) and RBM – two important concepts promoted in the ICH update – should not be understood as separate ideas but as two phases of the same RBQM paradigm. Both are focused on improving the operational success of clinical research, and both apply the core process of risk



assessment and risk mitigation. QBD represents the application of this process starting with the design of your research – and concepts such as patient-centricity and site-centricity completely align with QBD, which have the goal of increasing likelihood of successful research by carefully considering the plight of the patients and sites as a first step. QBD becomes RBM once a study protocol is finalized, at which point risk assessment is repeated with the goal of mitigating any remaining operational risks. Mitigation plans are then applied during study execution, which includes ongoing risk monitoring and a more targeted approach to site monitoring.

ESTABLISH YOUR RBM BUSINESS OBJECTIVES

An important first step towards ensuring sustainable success in your move to RBM, is to establish and confirm your organization's primary objectives; i.e., what is your organization trying to achieve with RBM? Each of the following three dimensions of RBM value should be considered:

1. **Improved Quality** – resulting in more reliable stage-gate decisions and faster time to market.
2. **Reduced Operational Costs** – particularly resulting from a more adaptive, targeted approach to site monitoring. The savings achieved can be very significant per study as RBM becomes fully implemented.
3. **Shorter Timelines** – specifically due to more effective enrollment and retention, along with a more efficient path to study database locks.

It will be additionally beneficial to identify and implement quantitative success measures to enable periodic assessment of the impact that your RBM implementation is having toward the stated objectives.

DEFINE YOUR APPROACH

RBM Implementation can be overwhelming for an organization given the wealth of information that is currently available. Starting simple is one way to maintain focus and concentrate on the elements of RBM that are most important to success. This principle applies not only to initial roll-out but as your organization reaches steady state and RBM becomes "business as usual" for the organization. A number of RBM early adopters in the industry have struggled to move forward effectively and one of the key factors conspiring against their success has been a level of RBM over-engineering that has resulted in complex, burdensome processes. Effective RBM implementation must be thoughtful, but it should be pragmatic and does not need to be burdensome. Some areas in particular to be aware of in this regard include the pre-study risk assessment and mitigation planning, the targeted SDV (and SDR) plan, and the centralized monitoring approach used for operational risk monitoring. The following are some considerations for each of these key areas.

Pre-Study Risk Planning – This is the most essential component of an RBM implementation, and perhaps the most prone to over-engineering and failure. A challenge that it presents to clinical development teams is the introduction of a new, poorly understood and poorly appreciated set of tasks to be completed on top of what is already a chaotic pre-study planning phase and a race to achieve the first-patient-in milestone date. The more time required of study team members to participate in the risk planning exercise, the more likely they will be to rush through it and "get it out of the way". The result is often a simple "box-checking" exercise that defeats the entire purpose and yields absolutely no value to the study. There are therefore two key considerations to address this challenge and ensure a successful, scalable roll-out of risk planning. First is to ensure that the process and associated tools are designed to not only effective at identifying and mitigating study risk, and simple to understand and efficient to complete. When done properly, there is no reason that a pre-study risk assessment and mitigation planning exercise should require more than a few hours of total time commitment from most study team representatives.

The second key consideration is to have in place a strong champion of the process embedded with each study team to train and coach them through the process, especially in the earlier stages of your RBM adoption. This person should be well-versed in the entire RBM process, passionate about its importance, and capable of clearly communicating its value to the study team.

SDV/SDR Planning – While not critical during initial roll-out of RBM, it is important for your organization to move steadily toward a significant reduction in reliance on SDV/SDR. Both SDV and SDR should be viewed as one method (in addition to centralized monitoring and other remote/centralized reviews) to confirm a site's compliance with GCP and the protocol, and adherence to good source records management, a concept. This confirmation can be achieved through a source review of just the first one or two patients enrolled at each site. Once a level of confidence has been established – and any observed findings addressed by the site – continued SDV/SDR should



be very limited and only used to periodically check (sample) to ensure the site's ongoing compliance. This periodic sampling of patient source records should focus on the most critical data domains.

There is also a temptation to assign different levels of SDV/SDR to sites at the beginning of a study based on some pre-determined site risk level (e.g., based on previous experience with a site, sites located in more GCP-naive regions, etc.). While this may at first appear an intelligent component of "risk-based" oversight, it actually fails to recognize the actual role of SDV/SDR in the new paradigm. SDV/SDR should not be thought of as a "hammer" to confirm the quality of all data at each site. Instead, it should be an initial and then very modestly-applied spot-check to help establish confidence in each site and/or identify emerging risk. A simpler, more rational and scalable approach is to roll out the same SDV/SDR plan to all sites at the beginning for each study, and only expand the scope of source review at a site for specific cause such as to further investigate and/or confirm resolution of some identified risks or issues. Such increases in scrutiny should themselves be applied modestly and not in a manner that condemns the site monitor to an unwarranted increase in SDV burden for the remainder of the study!

Achieving this fundamental change in the approach to SDV/SDR will enable site monitors to start changing their mindset and approach to focus more attention on what matters most during their site visits – including an ability to drive more productive site relationships and better site engagement. This will result not only in higher-quality outcomes but more effective patient recruitment and retention as well.

Centralized Monitoring – This is a critical component of operational success of RBM as it is a key new weapon for quality oversight. An effective centralized monitoring approach should include the following three components:

1. Statistical Data Monitoring (SDM)
2. Key Risk Indicators (KRIs)
3. Quality Tolerance Limits (QTLs)

Quality is much more important than quantity, especially as it relates to KRIs and QTLs. It should not be necessary to implement 30 or 40 KRIs for each study, which will be challenging to maintain and inevitably lead to duplicate risk detection and greater risk of "signal noise"; i.e., causing study teams to waste time chasing down false risk signals. Rather, identify a core set of appropriate KRIs, and focus on ensuring that these KRIs are optimized for earliest possible detection of risk and for minimizing likelihood of false alerting. The same principle should apply to QTLs, which should focus on the most important study-level risks; i.e., "failure points".

Statistical Data Monitoring (SDM) – also referred to as Centralized Statistical Monitoring (CSM) – has been under-appreciated by many organizations for the level of importance it has in effective quality oversight. While KRIs and QTLs are designed to monitor for pre-identified areas of risk, SDM can be effective at exposing various forms of study mis-conduct that may be more difficult to identify and/or characterize during pre-study risk planning. SDM works most effectively by running a discrete set of well-designed statistical tests across a broad swath of study data, in order to identify atypical patterns of data at various sites that represent potential mis-conduct, whether intentional or un-intentional. The forms of mis-conduct will range from outright fraud, to sloppiness, to training issues, and even to malfunctioning study equipment.

MANAGE CHANGE PRO-ACTIVELY

Change management is another key obstacle to successful roll-out of RBM, as it has been for any significant process or technology initiative (think of the transition from paper to EDC!). It is therefore highly important to begin change management planning as early as possible. And while many of the following considerations are no different for RBM than for any other change management initiative, they are nevertheless always worth repeating:

1. Secure full senior leadership buy-in and support. Without a clear, unified directive from the executive team, people in the organization will instinctively and unfortunately see that failure is an option. And because any disruption be perceived by many as a threat, behaviours will not align with success across the organization.
2. Identify RBM champions and appropriate early adopters (study teams) in the organization that can produce successful first use-cases to build momentum for the larger organization. Messaging is important as well in this regard, so terms like "Early Adoption" is much preferred to "RBM Pilot". The work "pilot" is generally taken as "experiment", which of course can fail. RBM cannot fail!
3. Develop an RBM Training and Communications plan, which should identify all stakeholders to be trained, the training modules to be developed and delivered, timing of training, etc. It should also identify the types and channels of communication in support of RBM roll-out. It will help tremendously in this regard to plan for strong, positive communications from senior leadership (as per #1 above).



4. Identify and focus particular attention on those stakeholders likely to be most resistant to an RBM paradigm. CRAs (site monitors) are typically the most directly impacted by RBM and therefore the most common source of resistance. It is important to stress the opportunity this presents to them, elevating their role in site management to a higher, more strategic level with less focus on the manually intensive SDV effort. The investigative sites themselves may express concerns, and appropriate communications should be developed to reassure them and dispel any mis-perceptions about what RBM involves for them (e.g., no need to fax or scan all of the patient source documents for remote review).

CONCLUSIONS

Besides now being a GCP expectation, RBM presents a tremendous opportunity for your organization to drive higher quality study outcomes, shorter study timelines, and all at a lower cost of development! Those who have achieved a successful roll-out of RBM and are approaching a “business-as-usual” environment, have enabled this success by applying thoughtful but simple processes, smart enabling technology, and a focus on change management. All of the key components of RBM implementation – including pre-study risk planning, adaptive site monitoring with a reduction in SDV/SDR, and centralized monitoring – do not need to be overly complex to be effective. And to the contrary, complexity impedes RBM effectiveness. A cornerstone principle of RBM methodology should also be a cornerstone principle to guide RBM implementation in your organization: “Focus on what matters.”

REFERENCES

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